Enantioselective auto- and cross catalytic reactions

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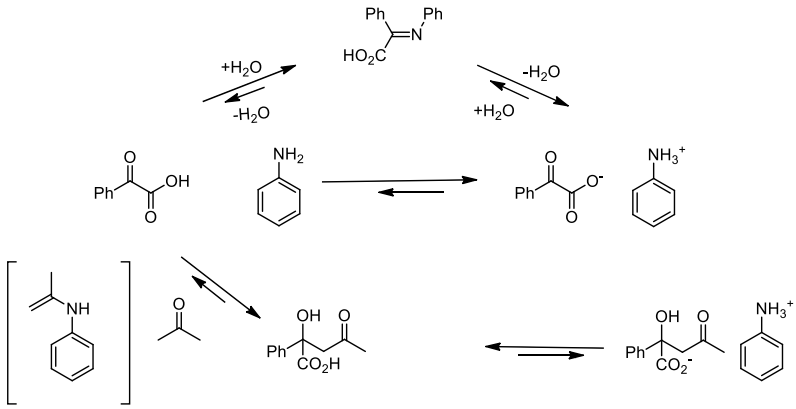
Summary

An understanding of how life began remains a formidable challenge thus driving considerable experimental research efforts in mimicking biological systems. Self-replication and homochirality are vital characteristics of living organisms. L-amino acids are one of the main carriers of homochirality in the living organisms. Many hypotheses were proposed to explain chemical pathway towards the asymmetric formation of chiral biomolecules such as amino acids. It has been proposed that in the earliest stages of life if small prebiotic molecules were catalytically active then small chiral imbalances would be amplified via auto-catalytic processes. In this research the main goal was to design a system for asymmetric autocatalytic synthesis of both quaternary and ternary amino acids. Next to that catalytic enantioselective synthesis of tetrahydroisoquinoline derivatives which are abundant motives in the structures of bioactive molecules and modern drugs was developed. Furthermore, extensive studies on the asymmetric amplification observed in the reaction of 1,2-addition of Grignard reagents to α,β-unsaturated ketones were undertaken.

In **Chapter 2**, a design of an autocatalytic system based on amino acids and experimental efforts are described. The goal was to take advantage of the bifunctional character of amino acids and to use them as autocatalysts to promote their own synthesis, starting from imino acid precursors. As a result of these studies, we found that the imino acid molecules, which were intended to be used as reagents for autocatalytic amino acid synthesis, are highly unstable and reactive: cyclic imino acids are prone to over-oxidation and linear imino acids are prone to hydrolase to the corresponding carbonyl compounds and amines, followed by salt formation. As a consequence of imino acid hydrolysis, fortunately we have discovered an interesting system, displaying an unusually slow release of a catalyst, trapped in the substrate molecule, for the synthesis of hydroxy acid compounds (Scheme 1). The results have been supported by kinetic studies and NMR analysis.



Scheme 1 - *Slow release of the catalyst in a self-replicating system.*

For racemic synthesis of hydroxy acids, catalyzed by aniline, we found that the product of the reaction has a significant rate-accelerating effect when used in combination with the aniline catalyst. As of now, the effect of the product on the reaction rate is uncertain and further studies are required. In addition, we have developed a proline catalyzed enantioselective synthesis of chiral hydroxy acids, with quaternary stereocenters, with enantioselectivities of up to 70% achieved.

In **Chapter 3**, the design of an asymmetric organocatalytic system has been proposed, based on a proline derivative. We have tried six approaches, involving different types of chemistry, use of Ni(I) complexes, IBX oxidation, Staudinger aza-Wittig reaction, etc... Unfortunately we were not able to isolate the pure desired product and test it in our envisioned autocatalytic Mannich reaction.

In **Chapter 4**, the development of an organocatalytic approach towards the synthesis of C-1 substituted tetrahydroisoquinolines and of an enamine based autocatalysis using isoquinolines motives, are described. Unfortunately, the Mannich product racemizes under the reaction conditions and, due to its unstable nature, decomposes after few hours. Protection of the free N-H group with a *t*-Boc group, and an acyl-Mannich reaction were performed in order to stabilize the product, however, only racemic compound was obtained. Further attempts to understand the pathway of the racemization process are needed in order to avoid this problem in future reactions.

In **Chapter 5**, we reported herein an organocatalytic asymmetric synthesis of tetrahydroisoquinoline derivatives promoted by L-proline. This methodology yields tricyclic *N*-heterocycles with good enantioselectivities, diastereselectivities, and yields, at a limited cost thanks to the use of L-proline. We found that the diastereoselectivity of the reaction is dependent on the enone used. Enones without any substituent in α-position or with two similar substituents led to the formation of racemic products.

Based on X-ray and 2D-NMR data we saw that aliphatic enones gave the formation of a product in which the major diastereoisomer is in *trans* conformation, while aromatic or heterocyclic enones give the *cis* product as a major diastereomer. These different reaction outcomes suggest that the reaction follows a different pathway depending on the enone that is used. Further mechanistic studies need to be performed.

Next to this main topic, we studied the origin of the asymmetric amplification in the 1,2-addition of Grignard reagents to α,β-unsaturated ketones (**Chapter 6**).

This phenomenon is not reaction or catalyst specific, but can be observed for metal complexes of a variety of chiral diphosphine ligands extensively used in asymmetric catalysis (Figure 1).

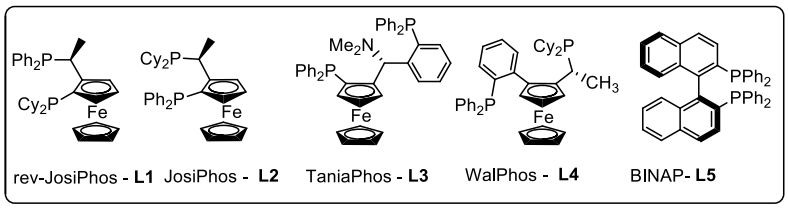


Figure 1 *- Structures of bidentate chiral phosphine ligands.*

We have found that complexation of a transition metal with chiral diphosphine ligands induces an extreme difference in the solubility between the racemates and the single enantiomers, an effect which is absent in the case of the free ligands (Figure 2).

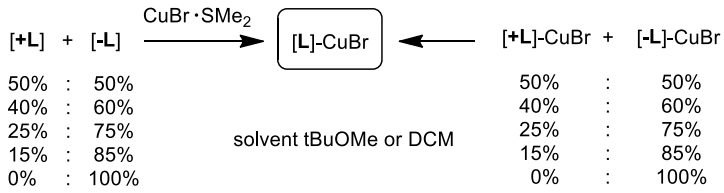


Figure 2 - *Preparation of scalemic copper complexes of L1.*

This phenomenon is responsible for a large asymmetric amplification observed in the 1,2-addition of Grignard reagents to enones and furthermore allows the efficient separation of racemic and enantiopure complexes from a scalemic mixture by simple filtration.

The metal complexation causes higher geometric rigidity of the complex, compared to the free ligands, which in turn enhances the differences in packing of racemic and enantiopure complexes.